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ASSISTED REPRODUCTION TECHNOLOGIES

# Women's morbid conditions are associated with decreased odds of live birth in the first IVF/ICSI treatment: a retrospective single-center study

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**Abstract**

**Purpose** The present study aims to ascertain whether there is a causal relationship between women's disease conditions present at the starting time of the first intended oocyte retrieval cycle and IVF/ICSI outcomes, primarily odds of live birth in the first IVF/ICSI treatment.

**Methods** This is a retrospective study of infertile healthy and diseased women that had a live birth and/or exhibited a complete first oocyte retrieval cycle. Generalized Estimating Equations (GEE) models were applied to adjust standard errors for the potential correlation among women exhibiting the same infertility etiology. Confounders to be controlled for in these GEE models were previously selected following a strict stepwise methodology.

**Results** Compared to healthy women, diseased women exhibited lower odds of live birth (OR (95% CI) 0.704 (0.576–0.860)). Further screening analyses indicated that subclinical iodine-deficiency hypothyroidism together with autoimmune thyroiditis contributed significantly to decrease odds of live birth (OR (95% CI) 0.720 (0.608–0.853)). Another important contribution arose from practically all the remaining morbid conditions analyzed. These diseases were individually associated with lower odds of live birth, although differences were non-significant. Notwithstanding, differences became significant after merging these diseases in a single group (OR (95% CI) 0.605 (0.394–0.930)).

**Conclusion** There is a significant causal association between most diseases present at the starting time of the first intended oocyte retrieval cycle and lower odds of live birth in the first IVF/ICSI treatment.

**Keywords** Disease conditions · Infertility etiology · In vitro fertilization · Cumulative live birth · Morbid conditions

## Introduction

It is known that infertility does not occur randomly in human populations. Instead, infertile individuals are clustered in discrete infertility etiologies that share particular genes and/or molecular pathways with other pathologies [1]. Moreover, infertility etiologies exhibit clinical relationships with other diseases appearing after infertility is manifested [1]. Thus, it is natural to think of each infertility etiology as just one more member of a larger meta-disease. For instance, women suffering from tubal factor share few genes, molecular pathways, or clinical traits with women exhibiting polycystic ovary syndrome (PCOS). In contrast, women suffering from PCOS share genes with other 23 diseases including gonadal dysgenesis, primary hypogonadism, type 2 diabetes mellitus with acanthosis nigricans, ovarian hyperstimulation syndrome, and precocious puberty (for references, see Tarín et al. [1]). The absence of connections among different infertility etiologies may have important implications for data analysis. For instance, "woman starting ovarian stimulation," "oocyte retrieval cycle," or "embryo transfer cycle" are usually considered as units of analysis in the field of Assisted Reproduction Technology (ART). These analyses do not adjust standard errors for the potential correlation among women exhibiting

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the same infertility etiology and, therefore, sample sizes are spuriously inflated [2].

Morbid conditions not only may appear after infertility is manifested, they may arise concomitantly or even before infertility is evidenced (e.g., diabetes mellitus or urinary tract infection). In this scenario, infertility may result from the morbid effects of preexisting or concomitant pathological conditions, independently of whether or not the particular infertility etiology shares genes and/or molecular pathways with these morbid conditions. Within this context, we should bear in mind that fertility and fecundity are two different but closely related terms. Fertility is defined as "the capacity to establish a clinical pregnancy," whereas fecundity is clinically defined as "the capacity to have a live birth" [3]. That is, a woman cannot be fecund unless she has previously been fertile. Consequently, many "infertile" women are not really infertile but infecund. This conceptual difference can be easily discriminated in women undergoing IVF/ICSI treatments. This population of women provides a unique opportunity to test whether preexisting or concomitant women's morbid conditions at the starting time of the first intended oocyte retrieval cycle are associated with both/either reduced fertility and/or fecundity. In any case, the primary or ultimate aim of IVF/ICSI treatments for "infertile" women is to have a live birth, i.e., to solve their problem of fecundity.

The present study aims to ascertain whether there is a causal relationship between women's disease conditions present at the starting time of the first intended oocyte retrieval cycle and IVF/ICSI outcomes, primarily odds of live birth in the first IVF/ICSI treatment.

## Methods

### Study design

This is a retrospective analysis of 933 IVF and 358 ICSI cycles from 1291 infertile couples enrolled in the Assisted Reproduction Unit of the Valencia University Clinic Hospital from January 2009 to December 2017. The study was exclusively focused on healthy and diseased women that underwent the first intended oocyte retrieval cycle in our center and had a live birth and/or exhibited a complete oocyte retrieval cycle with no frozen embryos left over for further transfers, i.e., the first oocyte retrieval cycle including the fresh and/or all the subsequent frozen-thawed embryo transfers. Note that both the Spanish Royal Decree-Law 1030/2006 and the Order SSI/2065/2014 establish that IVF treatment using own oocytes/spermatozoa or donated spermatozoa should be applied in the National Health System only if couples have not a common, previous, and healthy child. Accordingly, women that succeed in having a healthy live birth in a particular embryo transfer cycle did not experience further embryo transfers (in the event they had spare frozen embryos available for further transfers). No women with both an unhealthy live birth and spare frozen embryos available applied for further transfers. Thus, all the women entered into the study displayed either none or just a single episode of live birth. Live birth included the birth of at least one living child, regardless of the duration of gestation. All the stages of treatment from the start of ovarian stimulation to the outcome of the fresh and/or subsequent frozen embryo transfers were taken into consideration. For this reason, cycles canceled before either oocyte retrieval or embryo transfer were included into the final statistical analysis [4].

In order to control for the potential confounding effects that may be induced by men's medical conditions, only women whose oocytes were inseminated using sperm samples from healthy men were entered into the study. The term "healthy men" refers to non-diseased men in a good physical and mental condition irrespectively of whether or not they exhibited sperm anomalies. Table 1 displays the names and codes used to group women's medical conditions into chapters (indicated by Roman numerals). Names and codes were based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10 Version: 2016). Only ICD-10 chapters with sample sizes $\geq 10$ women were included in the study as distinct groups. ICD-10 chapters with sample sizes $< 10$ women were combined in a single "catch-all" group called "other diseases."

This study was approved by the Ethical Committee of Clinical Investigation, Valencia University Clinical Hospital on November 30th 2017 (2017/316). Written informed consent was not required from the participants because the retrospective nature of the study.

### Statistical analysis

Analysis of data was performed following a strict stepwise methodology. Firstly, the entire set of variables recorded in our Assisted Reproduction Unit database were revised to select potential confounders, i.e., those variables that occurred or were measured before both "woman's medical condition" (the "exposure") and six "IVF/ICSI outcomes" (the "outcomes"): "number of cycle cancellations before oocyte retrieval," "cumulative number of cycle cancellations before embryo transfer," "cumulative number of clinical pregnancies," "cumulative number of clinical pregnancy losses," "waiting time to the embryo transfer resulting in live birth," and "cumulative live birth." We should underline that the word "cumulative" refers to the sum of all the events taking place in the fresh and subsequent frozen cycles of the first intended oocyte retrieval cycle. Note that a confounder is defined as a variable that correlates (positively or negatively) with both the exposure and the outcome. In addition, a confounder should not be a mediator or intermediate variable

**Table 1** Names and ICD-10 codes used to classify women's medical conditions at the starting time of the first intended oocyte retrieval cycle

| Woman's medical condition | ICD-10 codes | Number of women ($n = 1291$) |
|---|---|---|
| Healthy | – | 962 |
| III. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | D50-D89 | 24 |
| Hemolytic anemias | D55-D59 | 11 |
| Primary thrombophilia-antiphospholipid antibody syndrome | D68.5-D68.6 | 11 |
| Purpura and other hemorrhagic conditions | D69 | 2 |
| IV. Endocrine, nutritional, and metabolic diseases | E00-E90 | 170 |
| Disorders of thyroid gland | E00-E07 | 148 |
| Subclinical iodine-deficiency hypothyroidism | E02 | 134 |
| Congenital hipothyroidism with diffuse goiter | E03.0 | 2 |
| Nontoxic single thyroid nodule | E04.1 | 1 |
| Nontoxic multinodular goiter | E04.2 | 1 |
| Thyrotoxicosis with diffuse goiter (Graves' disease) | E05.0 | 3 |
| Thyrotoxicosis, unspecified | E05.9 | 2 |
| Autoimmune thyroiditis | E06.3 | 5 |
| Diabetes mellitus | E10-E14 | 11 |
| Metabolic disorders | E70-E90 | 8 |
| Disorders of fructose metabolism | E74.1 | 1 |
| Other disorders of intestinal carbohydrate absorption | E74.3 | 1 |
| Hypercholesterolemia | E78 | 5 |
| Gilbert syndrome | E80.4 | 1 |
| Postprocedural endocrine and metabolic disorders, not elsewhere classified | E89 | 3 |
| Postprocedural hypothyroidism | E89.0 | 3 |
| V. Mental and behavioral disorders | F00-F99 | 16 |
| Bipolar affective disorder | F31 | 1 |
| Depressive episode | F32 | 10 |
| Other anxiety disorders | F41 | 5 |
| VI. Diseases of the nervous system | G00-G99 | 24 |
| Encephalitis, myelitis, and encephalomyelitis | G04 | 1 |
| Multiple sclerosis | G35 | 5 |
| Epilepsy | G40 | 3 |
| Migraine | G43 | 14 |
| Myasthenia gravis | G70.0 | 1 |
| IX. Diseases of the circulatory system | I00-I99 | 18 |
| Valvular heart disease | I08 | 1 |
| Essential (primary) hypertension | I10 | 11 |
| Cardiomyopathy | I42 | 3 |
| Other conduction disorders | I45 | 1 |
| Cerebral aneurysm, nonruptured | I67.1 | 1 |
| Raynaud syndrome | I73.0 | 1 |
| X. Diseases of the respiratory system | J00-J99 | 23 |
| Asthma | J45 | 23 |
| XI. Diseases of the digestive system | K00-K93 | 14 |
| Gastro-esophageal reflux disease | K21 | 1 |
| Gastritis, unspecified | K29.7 | 1 |
| Crohn's disease (regional enteritis) | K50 | 4 |
| Ulcerative colitis | K51 | 4 |
| Allergic and dietetic gastroenteritis and colitis | K52.2 | 1 |

**Table 1** (continued)

| Woman's medical condition | ICD-10 codes | Number of women ($n = 1291$) |
|---|---|---|
| Irritable bowel syndrome | K58 | 2 |
| Hemorrhoids and perianal venous thrombosis | K64 | 1 |
| XIII. Diseases of the musculoskeletal system and connective tissue | M00-M99 | 12 |
| Rheumatoid arthritis, unspecified | M06.9 | 6 |
| Systemic lupus erythematosus | M32 | 2 |
| Systemic involvement of connective tissue, unspecified | M35.9 | 2 |
| Fibromyalgia | M79.7 | 2 |
| Other diseases | – | 28 |
| I Certain infectious and parasitic diseases | A00-B99 | 7 |
| Anogenital (venereal) warts | A63.0 | 1 |
| Chronic viral hepatitis B NOS | B18.1 | 6 |
| II Neoplasms | C00-D48 | 5 |
| Carcinoma in situ: thyroid and other endocrine glands | D09.3 | 1 |
| Benign neoplasm of liver | D13.4 | 1 |
| Benign neoplasm of breast | D24 | 1 |
| Benign neoplasm of ovary | D27 | 2 |
| XII. Diseases of the skin and subcutaneous tissue | L00-L99 | 4 |
| Psoriasis | L40 | 3 |
| Vitiligo | L80 | 1 |
| XIV. Diseases of the genitourinary system | N00-N99 | 2 |
| Unspecified nephritic syndrome | N05 | 1 |
| Chronic kidney disease | N18 | 1 |
| XVI. Certain conditions originating in the perinatal period | P00-P96 | 1 |
| Cardiac murmurs and other cardiac sounds originating in the perinatal period | P29.8 | 1 |
| XVII. Congenital malformations, deformations, and chromosomal abnormalities | Q00-Q99 | 2 |
| Hirschsprung disease | Q43.1 | 1 |
| Neurofibromatosis | Q85.0 | 1 |
| XVIII. Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified | R00-R99 | 1 |
| Elevation of levels of transaminase and lactic acid dehydrogenase (LDH) | R74.0 | 1 |
| Multiple diseases | – | 6 |
| Papillary thyroid cancer/thyrotoxicosis with toxic multinodular goiter | D09.3/E05.2 | 1 |
| Hypothyroidism, unspecified/metabolic disorder, unspecified | E03.9/E88.9 | 1 |
| Hypothyroidism, unspecified/disorders of urea cycle metabolism | E03.9/E72.2 | 1 |
| Disorder of thyroid, unspecified/multiple sclerosis | E07.9/G35 | 1 |
| Other hypoglycemia/essential (primary) hypertension/asthma | E16.1/I10/J45 | 1 |
| Lactose intolerance, unspecified/disorders of fructose metabolism | E73.9/E74.1 | 1 |

located along the causal pathway between the exposure and the outcome. It must occur or be measured before the exposure variable [5, 6]. Special attention was paid to discard inadequate variables that did not meet the criteria for confounding because inclusion of these variables may cause distorted or incorrect estimate of potential association between exposure and outcome variables.

Independent-samples *t* test and chi-square test were applied to analyze continuous and categorical epidemiological variables, respectively. Generalized Estimating Equations (GEE) models were used to ascertain whether there is a causal relationship between women's disease conditions present at the starting time of the first intended oocyte retrieval cycle and IVF/ICSI outcomes. These models allow for analysis of repeated measurements or other correlated observations such as clustered data, especially when they are binary or in the form of counts [2]. Variables were arranged in a hierarchical two-level structure with "woman starting ovarian stimulation" clustered within "female infertility etiology." These hierarchical structures adjusted standard errors for the potential correlation among women exhibiting the same cause of infertility. Table 2 shows the clusters of women established according their infertility etiology.

Distinct combinations of MODEL distribution and LINK function were selected depending on whether the response variable was binary or in the form of counts. Specifically, BINOMIAL distribution and LOGIT link function for binary variables, and POISSON distribution and LOG link function for count variables. The ROBUST variance estimator (a.k.a. the Huber/White/sandwich estimator) was the method used to compute the variance-covariance matrix of the regression parameter coefficients. The goodness-of-fit Quasi-likelihood under Independence Model Criterion (QIC) was used to choose between two working correlation structures: EXCHANGABLE and INDEPENDENT. The EXCHANGABLE matrix (1's on the diagonal and equal correlation for all off-diagonal elements) assumes that the correlations between different members of a particular cluster are the same. For instance, correlation between woman 1 and 2 within a given level of female infertility etiology is the same than correlation between woman 3 and 5. In contrast, the INDEPENDENT matrix (1's on the diagonal and zeros for all off-diagonal elements) assumes that there is no correlation between different members of a specific cluster. The working correlation structure that had the smallest QIC was considered as the matrix that provided the best goodness of fit [7]. This matrix was selected and used for data analysis.

It is known that testing more than one hypothesis at a time may increase the probability of finding spurious significant results [8]. Consequently, the seminal sequential procedure by Benjamini and Hochberg [9] was applied to control for false discovery rate (the expected fraction of tests that are declared significant in a study despite the null hypotheses are true) and adjust the $P$ value [10]. Values shown in the text and tables are raw/uncorrected means ± standard errors (SEs), marginal/corrected means ± SEs, regression coefficients ± SEs, and exponentiated regression coefficients and their respective 95% confidence intervals (CIs). Note that exponentiated regression coefficients should be interpreted as odds ratios (ORs, ratios between two odds) or rate ratios (RRs, ratios between two incidence rates) depending on whether logistic or Poisson regression is applied, respectively [11]. If the independent variable is categorical, exponentiated regression coefficients specify the estimated OR or RR of the dependent variable for a given category of the independent variable versus a reference category. In contrast, when the independent variable is continuous, they designate the estimated OR or RR of the dependent variable for one-unit change in the independent variable. All the analyses were carried out using the Statistical Package for Social Sciences (IBM SPSS Statistics, version 24; © Copyright IBM Corporation and its licensors 1989, 2016).

## Results

Table 3 shows epidemiological data of the couples entered into the study, stratified by the women's medical condition present at the starting time of the first intended oocyte retrieval cycle. Only women's age and body mass index (BMI) were entitled to be preselected as potential confounders. We may assume that these variables (1) occurred before both woman's medical condition and the six IVF/ICSI outcomes analyzed, (2) were positively associated with woman's medical condition, and (3) were not mediators or intermediate variables located along the causal pathway between the exposure and the outcomes. The remaining variables shown in Table 3 did not satisfy these preliminary requirements and were excluded.

Table 4 displays the results of the 12 tests applied to determine whether the two preselected potential confounders were also significantly associated with the six IVF/ICSI outcomes analyzed. Women's age was significantly associated with cumulative number of clinical pregnancies (RR (95% CI) 0.953 (0.928–0.978)) and cumulative live birth (OR (95% CI) 0.914

**Table 2** Clusters of women established according their infertility etiology

| Infertility etiology | Medical condition | | |
|---|---|---|---|
| | Healthy ($n = 962$) | Diseased ($n = 329$) | Total ($n = 1291$) |
| Tubal factor | 7.3 (70)[a] | 5.2 (17) | 6.7 (87) |
| Uterine factor | 12.5 (120) | 13.1 (43) | 12.6 (163) |
| Endometriosis | 5.4 (52) | 4.9 (16) | 5.3 (68) |
| Ovulatory dysfunction | 9.9 (95) | 9.7 (32) | 9.8 (127) |
| Diminished ovarian reserve | 10.4 (100) | 9.4 (31) | 10.1 (131) |
| Unknown factor | 27.7 (266) | 22.2 (73) | 26.3 (339) |
| Multiple female factors | 25.4 (244) | 33.1 (109) | 27.3 (353) |
| Other factors | 1.6 (15) | 2.4 (8) | 1.8% (23) |

Data are stratified by women's medical condition, two-sided Pearson chi-square test: $P \leq 0.126$

[a] Values are percentages and number of women used to calculate these percentages in parentheses

**Table 3** Epidemiological data of the couples entered into the study, stratified by medical condition present at the starting time of the first intended oocyte retrieval cycle

| Potential confounders | Medical condition | | | |
|---|---|---|---|---|
| | Healthy (*n* = 962) | Diseased (*n* = 329) | *P* | Total (*n* = 1291) |
| Women's age (years) | 34.974 ± 0.102 (28–41)[a] | 35.556 ± 0.171 (28–41) | 0.004 | 35.122 ± 0.088 (28–41) |
| Women's BMI | 22.981 ± 0.113 (16.140–51.780) | 23.682 ± 0.229 (17.040–42.240) | 0.003 | 23.159 ± 0.103 (16.140–51.780) |
| Women's tobacco smoking[b] | 3.780 ± 0.221 (0–25) | 3.283 ± 0.349 (0–25) | 0.248 | 3.653 ± 0.188 (0–25) |
| Duration of infertility (years) | 2.677 ± 0.049 (0–10) | 2.606 ± 0.091 (0–13) | 0.479 | 2.659 ± 0.043 (0–13) |
| Type of menstrual cycle | | | 0.030 | |
| Regular | 85.3 (821)[c] | 86.6 (285) | | 85.7 (1106/1291) |
| Irregular | 14.0 (135) | 11.2 (37) | | 13.3 (172/1291) |
| Amenorrhea | 0.6 (6) | 2.1 (7) | | 1.0 (13/1291) |
| Number of antral follicles | 15.481 ± 0.2875 1 (0–71) | 15.365 ± 0.480 (3–60) | 0.837 | 15.452 ± 0.247 (1–71) |
| Basal AMH (ng/mL) | 2.287 ± 0.0541 (0.0–27.0) | 2.101 ± 0.0639 (0.1–8.1) | 0.063 | 2.240 ± 0.044 (0–27) |
| Basal FSH (mUI/mL) | 7.084 ± 0.102 (0.9–66.7) | 7.438 ± 0.409 (0.1–106.0) | 0.232 | 7.174 ± 0.129 (0.1–106.0) |
| Basal LH (mUI/mL) | 6.684 ± 0.131 (1.0–57.0) | 6.480 ± 0.421 (0.1–133.0) | 0.540 | 6.632 ± 0.1450 (0.1–133.0) |
| Basal $E_2$ (pg/mL) | 53.053 ± 1.045 (2.2–321.0) | 49.940 ± 1.556 (0.1–258.0) | 0.121 | 52.260 ± 0.746 (0.1–321.0) |
| Basal TSH (μUI/mL) | 2.344 ± 0.171 (0.15–136.00) | 2.324 ± 0.069 (0.01–150.00) | 0.945 | 2.340 ± 0.129 (0.01–136.00) |
| Male infertility etiology | | | 0.329 | |
| Donor sperm | 1.8 (17) | 1.5 (5) | | 1.7 (22) |
| Oligo, asteno-, and/or teratozoospermia | 44.4 (427) | 39.8 (131) | | 43.2 (558) |
| Cryptozoospermia or azoospermia | 12.6 (121) | 11.6 (38) | | 12.3 (159) |
| Unknown (normozoospermia) | 41.3 (397) | 47.1 (155) | | 42.8 (552) |

The adjusted/corrected Benjamini and Hochberg's significance is $P \leq 0.008$, based on 12 statistical tests applied

[a] Values are raw means ± SEs. Minimum and maximum values are given in parentheses

[b] Number of cigarettes smoked per day for the 3 months before starting the first intended oocyte retrieval cycle

[c] Values are percentages and number of women used to calculate these percentages in parentheses

(0.879–0.952)). Likewise, women's BMI was significantly associated with cumulative number of cycle cancelations before embryo transfer (RR (95% CI) 1.011 (1.002–1.020)), and cumulative number of clinical pregnancies (RR (95% CI) 0.978 (0.969–0.986)). Hence, both women's age and/or women's BMI were finally selected as true confounders to be controlled for in subsequent analyses.

The output of these analyses is shown in Table 5. Data indicate that diseased women exhibited significantly higher cumulative number of cycle cancelations before embryo transfer (RR (95% CI) 1.552 (1.314–1.833)) and waiting time to the embryo transfer resulting in live birth (RR (95% CI) 2.467 (1.769–3.440)) compared to healthy women (the reference group). Inversely, odds of cumulative live birth were significantly lower in diseased women (OR (95% CI) 0.704 (0.576–0.860)).

Further analyses were performed to find out which particular ICD-10 chapter(s) contributed to generate these significant effects. The resulting analyses indicated that "endocrine, nutritional and metabolic diseases" was the only ICD-10 chapter significantly associated with both a higher cumulative number of cycle cancelations before embryo transfer (RR (95% CI) 1.739 (1.403–2.154)) and lower odds of cumulative live birth (OR (95% CI) 0.719 (0.564–0.917)) (Table 6). Note, however, that all the remaining ICD-10 chapters, except "Mental and behavioral disorders," were associated with lower odds of cumulative live birth, although differences were non-significant. Thus, an additional analysis was applied to determine whether differences became significant after merging these ICD-10 chapters in a single group. This analysis indicated that the merged group (all the ICD-10 chapters analyzed except "endocrine, nutritional and metabolic diseases" and "Mental and behavioral disorders") exhibited significantly ($P \leq 0.022$) lower odds of cumulative live birth than healthy women (OR (95% CI) 0.605 (0.394–0.930), adjusted by woman's age: $P \leq 0.0005$).

Additional analyses were applied to uncover the particular disease category(ies) within the ICD-10 chapter "endocrine, nutritional and metabolic diseases" responsible for the significant effects reported in Table 6. These analyses revealed that only women suffering from disorders of the thyroid gland displayed both a significantly higher cumulative number of

**Table 4** Effect of potential confounders on IVF/ICSI outcomes

| Potential confounder | IVF/ICSI outcome | | | | | |
|---|---|---|---|---|---|---|
| | Cycle cancelation before oocyte retrieval ($n = 1291$)[a] | Cumulative number of cycle cancelations before embryo transfer ($n = 1291$)[a] | Cumulative number of clinical pregnancies ($n = 1291$)[a] | Cumulative number of clinical pregnancy losses ($n = 495$)[a] | Waiting time (weeks) to the embryo transfer resulting in live birth ($n = 399$)[a] | Cumulative live birth ($n = 1291$)[b] |
| Age (years) | $P \leq 0.025$ | $P \leq 0.209$ | $P \leq 0.0005$ | $P \leq 0.085$ | $P \leq 0.267$ | $P \leq 0.0005$ |
| | $0.100 \pm 0.044$[c] | $0.024 \pm 0.019$ | $-0.048 \pm 0.013$ | $0.042 \pm 0.024$ | $0.021 \pm 0.019$ | $-0.089 \pm 0.020$ |
| | 1.105 (1.013–1.205)[d] | 1.024 (0.987–1.063) | 0.953 (0.928–0.978) | 1.043 (0.994–1.093) | 1.022 (0.984–1.061) | 0.914 (0.879–0.952) |
| BMI | $P \leq 0.088$ | $P \leq 0.015$ | $P \leq 0.0005$ | $P \leq 0.983$ | $P \leq 0.420$ | $P \leq 0.086$ |
| | $0.018 \pm 0.011$ | $0.011 \pm 0.005$ | $-0.023 \pm 0.004$ | $-0.001 \pm 0.036$ | $0.030 \pm 0.037$ | $-0.031 \pm 0.018$ |
| | 1.018 (0.997–1.040) | 1.011 (1.002–1.020) | 0.978 (0.969–0.986) | 0.999 (0.931–1.072) | 1.030 (0.958–1.107) | 0.969 (0.935–1.004) |

The adjusted/corrected Benjamini and Hochberg's significance is $P \leq 0.017$, based on 12 statistical tests applied

[a] Count variable that records total number of events per woman using the embryos generated in the first intended oocyte retrieval cycle

[b] Binomial variable that considers the occurrence = 1 or non-occurrence = 0 of an event

[c] Values are regression coefficients ± SEs

[d] Values are exponentiated regression coefficients. Their respective 95% CIs are given in parentheses

cycle cancelations before embryo transfer (RR (95% CI) 1.682 (1.396–2.025)) and significantly lower odds of cumulative live birth (OR (95% CI) 0.748 (0.623–0.897)) (Table 7).

Table 1 indicates that the vast majority of women suffering from disorders of the thyroid gland displayed subclinical iodine-deficiency hypothyroidism (90.5%, 134/148) or autoimmune thyroiditis (3.4%, 5/148). Consequently, we may assume that these disorders contributed the most to the adverse IVF/ICSI outcomes of women suffering from disorders of the thyroid gland. In order to test this hypothesis, we performed a final analysis focusing exclusively on healthy and diseased women suffering from subclinical iodine-deficiency hypothyroidism or autoimmune thyroiditis. Similar outcomes to those reported in Table 7 were found. Specifically, a significantly ($P \leq 0.0005$) higher cumulative number of cycle cancelations before embryo transfer (RR (95% CI) 1.662 (1.370–2.017), adjusted by woman's BMI: $P \leq 0.039$) and significantly ($P \leq 0.0005$) lower odds of cumulative live birth (OR (95% CI) 0.720 (0.608–0.853), adjusted by woman's age: $P \leq 0.0005$). In addition, these diseased women exhibited a significantly ($P \leq 0.018$) lower cumulative number of clinical pregnancy losses compared to healthy women (RR (95% CI) 0.548 (0.327–0.917)).

We should note that, on most occasions, the EXCHANGABLE working correlation matrix consistently provided smaller QIC values (better goodness-of-fit) than the INDEPENDENT matrix. The only exceptions were found when analyzing the effects of potential confounders and women's medical condition on cumulative number of cycle cancelations before either oocyte retrieval or embryo transfer. In these particular GEE models, the INDEPENDENT working correlation matrix provided lower QIC values than the EXCHANGABLE structure.

## Discussion

The present study shows a significant negative relationship between women's disease conditions at the starting time of the first intended oocyte retrieval cycle and odds of live cumulative birth in the first IVF/ICSI treatment. That is, women's morbid conditions, irrespective of whether or not these morbid conditions share genes, molecular pathways, and/or clinical relationships with women's infertility etiologies, were associated with lower odds of cumulative live birth, i.e., lower fecundity potential, in the first IVF/ICSI treatment. Other secondary IVF/ICSI outcomes related with women's fertility and fecundity potential were also impaired, specifically, higher cumulative number of cycle cancelations before embryo transfer and longer waiting times to the embryo transfer resulting in live birth. Additional screening analyses indicated that the negative effects on odds of cumulative live birth were basically associated with endocrine, nutritional, and

**Table 5** Effect of medical condition present in women at the starting time of the first intended oocyte retrieval cycle on IVF/ICSI outcomes after adjusting for “women’s age” and/or “women’s BMI”

| Explanatory variables | IVF/ICSI outcome | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | Cycle cancelation before oocyte retrieval[a] | *n* | Cumulative number of cycle cancelations before embryo transfer[b] | *n* | Cumulative number of clinical pregnancies[b] | *n* | Cumulative number of clinical pregnancy losses[b] | *n* | Waiting time (weeks) to the embryo transfer resulting in live birth[b] | *n* | Cumulative live birth[a] |
| Medical condition[a] | 1291 | $P \leq 0.307$ | 1291 | $P \leq 0.0005$ | 1291 | $P \leq 0.066$ | 495 | $P \leq 0.530$ | 399 | $P \leq 0.0005$ | 1291 | $P \leq 0.001$ |
| Healthy | 962 | 0.066 ± 0.022[c]<br>1 | 962 | 0.172 ± 0.017<br>1 | 962 | 0.405 ± 0.023<br>1 | 389 | 0.169 ± 0.012<br>1 | 318 | 3.540 ± 0.568<br>1 | 962 | 0.330 ± 0.019<br>1 |
| Diseased | 329 | 0.082 ± 0.013<br>1.253 (0.813–1.932)[d] | 329 | 0.267 ± 0.017<br>1.552 (1.314–1.833) | 329 | 0.342 ± 0.021<br>0.844 (0.705–1.011) | 106 | 0.199 ± 0.051<br>1.176 (0.709–1.951) | 81 | 8.740 ± 1.025<br>2.467 (1.769–3.440) | 329 | 0.250 ± 0.018<br>0.704 (0.576–0.860) |
| Age (years) | – | – | – | – | 1291 | $P \leq 0.001$<br>−0.046 ± 0.0136<br>0.955 (0.930–0.981) | – | – | – | – | 1291 | $P \leq 0.0005$<br>−0.086 ± 0.020<br>0.917 (0.882-0.954) |
| BMI | – | – | 1291 | $P \leq 0.170$<br>0.007 ± 0.005<br>1.007 (0.997–1.016) | 1291 | $P \leq 0.0005$<br>−0.019 ± 0.004<br>0.981 (0.973–0.989) | – | – | – | – | – | – |

The adjusted/corrected Benjamini and Hochberg’s significance is $P \leq 0.037$, based on 26 statistical tests applied

[a] Binary variable that takes into account the occurrence = 1 or non-occurrence = 0 of an event

[b] Count variable that records the total number of events per woman using the embryos generated in the first intended oocyte retrieval cycle

[c] Values are either marginal means ± SEs in the two categories of “medical condition” or regression coefficients ± SEs of “women’s age” and “women’s BMI”

[d] Values are exponentiated regression coefficients. Their respective 95% CIs are given in parentheses

**Table 6** Effect of disease categories present in women at the starting time of the first intended oocyte retrieval cycle on those IVF/ICSI outcomes shown in Table 5 that were simultaneously significant

| Explanatory variables | IVF/ICSI outcome | | | | | |
|---|---|---|---|---|---|---|
| | $n$ | Cumulative number of cycle cancelations before embryo transfer[a] | $n$ | Waiting time (weeks) to the embryo transfer resulting in live birth[a] | $n$ | Cumulative live birth[b] |
| Medical condition[a] | 1291 | $P \leq 0.0005$ | 399 | $P \leq 0.0005$ | 1291 | $P \leq 0.0005$ |
| Healthy | 962 | 0.172 ± 0.017[c]<br>1 | 318 | 3.550 ± 0.562<br>1 | 962 | 0.330 ± 0.019<br>1 |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 24 | $P \leq 0.930$<br>0.166 ± 0.065<br>0.965 (0.442–2.110)[d] | 5 | $P \leq 0.018$<br>31.850 ± 29.597<br>8.982 (1.459–55.299) | 24 | $P \leq 0.040$<br>0.200 ± 0.047<br>0.526 (0.285–0.971) |
| Endocrine, nutritional, and metabolic diseases | 170 | $P \leq 0.0005$<br>0.299 ± 0.037<br>1.739 (1.403–2.154) | 42 | $P \leq 0.150$<br>5.950 ± 1.814<br>1.679 (0.829–3.401) | 170 | $P \leq 0.008$<br>0.260 ± 0.030<br>0.719 (0.564–0.917) |
| Mental and behavioral disorders | 16 | $P \leq 0.254$<br>0.063 ± 0.053<br>0.367 (0.066–2.051) | 7 | 0.000 ± 0.000<br>–<br>– | 16 | $P \leq 0.101$<br>0.450 ± 0.078<br>1.667 (0.905–3.073) |
| Diseases of the nervous system | 24 | $P \leq 0.035$<br>0.374 ± 0.138<br>2.177 (1.058–4.483) | 6 | $P \leq 0.043$<br>7.700 ± 2.978<br>2.171 (1.026–4.590) | 24 | $P \leq 0.280$<br>0.250 ± 0.052<br>0.696 (0.360–1.344) |
| Diseases of the circulatory system | 18 | $P \leq 0.939$<br>0.165 ± 0.094<br>0.958 (0.318–2.888) | 3 | 0.000 ± 0.000<br>–<br>– | 18 | $P \leq 0.061$<br>0.180 ± 0.072<br>0.442 (0.188–1.039) |
| Diseases of the respiratory system | 23 | $P \leq 0.397$<br>0.216 ± 0.040<br>1.257 (0.740–2.136) | 5 | $P \leq 0.0005$<br>26.020 ± 10.803<br>7.339 (2.922–18.435) | 23 | $P \leq 0.469$<br>0.230 ± 0.106<br>0.625 (0.175–2.230) |
| Diseases of the digestive system | 14 | $P \leq 0.279$<br>0.287 ± 0.126<br>1.670 (0.660–4.224) | 3 | $P \leq 0.0005$<br>0.350 ± 0.161<br>0.099 (0.037–0.262) | 14 | $P \leq 0.469$<br>0.220 ± 0.130<br>0.572 (0.126–2.596) |
| Diseases of the musculoskeletal system and connective tissue | 12 | $P \leq 0.440$<br>0.082 ± 0.077<br>0.480 (0.075–3.085) | 4 | $P \leq 0.923$<br>3.250 ± 2.526<br>0.917 (0.158–5.333) | 12 | $P \leq 0.992$<br>0.320 ± 0.113<br>0.994 (0.339–2.913) |
| Other diseases | 28 | $P \leq 0.0005$<br>0.358 ± 0.046<br>2.084 (1.504–2.887) | 6 | $P \leq 0.0005$<br>18.130 ± 3.299<br>5.112 (3.290–7.944) | 28 | $P \leq 0.091$<br>0.220 ± 0.059<br>0.585 (0.314–1.089) |
| Age (years) | – | – | – | – | 1291 | $P \leq 0.0005$<br>−0.087 ± 0.020<br>0.917 (0.882–0.954) |
| BMI | 1291 | $P \leq 0.110$<br>0.007 ± 0.004<br>1.007 (0.998–1.016) | – | – | – | – |

The adjusted/corrected Benjamini and Hochberg's significance is $P \leq 0.037$, based on 26 statistical tests applied

[a] Count variable that records the total number of events per woman using the embryos generated in the first intended oocyte retrieval cycle

[b] Binary variable that takes into account the occurrence = 1 or non-occurrence = 0 of live birth

[c] Values are either marginal means ± SEs in the different categories of "medical condition" or regression coefficients ± SEs of "women's age" and "women's BMI"

[d] Values are exponentiated regression coefficients. Their respective 95% CIs are given in parentheses

**Table 7** Effect of endocrine, nutritional, and metabolic diseases present in women at the starting time of the first intended oocyte retrieval cycle on those IVF/ICSI outcomes shown in Table 6 that were simultaneously significant

| Explanatory variables | IVF/ICSI outcome | | | |
|---|---|---|---|---|
| | *n* | Cumulative number of cycle cancelations before embryo transfer[a] | *n* | Cumulative live birth[b] |
| Medical condition | 1132 | $P \leq 0.0005$ | 1132 | $P \leq 0.014$ |
| Healthy | 962 | 0.172 ± 0.017[c]<br>1 | 962 | 0.330 ± 0.018<br>1 |
| Disorders of thyroid gland | 148 | $P \leq 0.0005$<br>0.289 ± 0.030<br>1.682 (1.396–2.025)[d] | 148 | $P \leq 0.002$<br>0.270 ± 0.024<br>0.748 (0.623–0.897) |
| Diabetes mellitus | 11 | $P \leq 0.0005$<br>0.442 ± 0.130<br>2.572 (1.514–4.370) | 11 | $P \leq 0.218$<br>0.120 ± 0.112<br>0.270 (0.034–2.167) |
| Metabolic disorders + postprocedural endocrine and metabolic disorders, not elsewhere classified | 11 | $P \leq 0.006$<br>0.267 ± 0.036<br>1.554 (1.138–2.122) | 11 | $P \leq 0.866$<br>0.300 ± 0.133<br>0.896 (0.248–3.231) |
| Age (years) | – | – | 1132 | $P \leq 0.0005$<br>−0.083 ± 0.016<br>0.920 (0.891–0.950) |
| BMI | 1132 | $P \leq 0.059$<br>0.011 ± 0.006<br>1.012 (1.000–1.024) | – | – |

The adjusted/corrected Benjamini and Hochberg's significance is $P \leq 0.037$, based on 26 statistical tests applied

[a] Count variable that records the total number of cycle cancelations before embryo transfer per woman using the embryos generated in the first intended oocyte retrieval cycle

[b] Binary variable that takes into account the occurrence = 1 or non-occurrence = 0 of live birth

[c] Values are either marginal means ± SEs in the different categories of "medical condition" or regression coefficients ± SEs of "women's age" and "women's BMI"

[d] Values are exponentiated regression coefficients. Their respective 95% CIs are given in parentheses

metabolic diseases disorders, in particular, subclinical iodine-deficiency hypothyroidism and autoimmune thyroiditis. Notwithstanding, another important contribution arose from practically all the remaining ICD-10 chapters analyzed. These chapters were individually associated with lower odds of cumulative live birth. Note, however, that differences were non-significant compared to healthy women most likely due to the relative low incidence of these diseases in the population. Not surprisingly, differences became significant after merging together these ICD-10 chapters in a single group. Women suffering from mental and behavioral disorders did not follow the general trend displayed by the remaining ICD-10 chapters. Instead, they exhibited higher, although non-significant, odds of cumulative live birth compared to healthy women. The present study also demonstrates, for the first time, that it is necessary to control for the potential correlation among women displaying the same infertility etiology. Actually, in the majority of tests applied, the EXCHANGABLE working correlation matrix consistently provided better goodness-of-fit than the INDEPENDENT matrix. In addition, the present data indicate that women's disease condition at the starting time of the first intended oocyte retrieval cycle should be considered as a potential confounder and controlled for in future studies. Unfortunately, this variable is usually disregarded in ART studies.

Recent systematic reviews and meta-analyses [12–14] provide inconsistent conclusions about the potential negative effects of subclinical iodine-deficiency hypothyroidism and/or thyroid autoimmunity on IVF/ICSI outcomes, including increased risks of miscarriage and decreased odds of live birth. In the present study, women suffering from subclinical iodine-deficiency hypothyroidism or autoimmune thyroiditis displayed not only a higher cumulative number of cycle cancelations before embryo transfer and lower odds of cumulative live birth, but also lower cumulative number of clinical pregnancy losses.

As mentioned above, women suffering from mental and behavioral disorders exhibited non-significant higher odds of cumulative live birth compared to healthy women. All these women ($n = 16$) were taking antidepressants at the starting time of the first oocyte retrieval cycle. The most used antidepressants were non-selective serotonin reuptake inhibitors (non-SSRIs) (75.0% (12/16) of all the women suffering from mental and behavioral disorders, and 85.7% (6/7) of women suffering from mental and behavioral disorders that had a live birth). Accordingly, these data are not in line with a nationwide register-based cohort study of 23.557 women undergoing their first IVF cycle [15] reporting significant negative effects of non-SSRIs on odds of live birth. Differences in sample size between the present and the nationwide register-based cohort study [15] may explain discrepancies between studies.

As far as we are aware, there is a nearly total absence of IVF/ICSI studies aimed to ascertain the effects on odds of live birth of those disease categories reported in the present study exhibiting the general trend of being associated with lower odds of cumulative live birth (see Table 6). The only exception is "Primary thrombophilia-antiphospholipid antibody syndrome." Literature reports inconsistent associations between thrombophilia and IVF outcomes (for references, see Di Nisio et al. [16]). However, a recent study [16] has found a non-significant trend towards lower live birth percentages and higher risk of spontaneous abortion in women suffering from either individual or multiple inherited and acquired thrombophilic defects compared with women without thrombophilia.

Taking into account the retrospective design of the present study, one of the major strengths of this study lies in the strict stepwise methodology followed to select true confounders to be controlled for in the GEE models applied. This methodology should be implemented in ART studies to avoid distorted or incorrect estimations of potential association between exposure and outcome variables. Another strength of the study is based on the fact that all the data included in the study come from a single center. This has the advantage of reducing heterogeneity among women due to genetic and environmental factors as well as infertility treatments and/or laboratory procedures.

Despite this study includes 1291 women that underwent their first IVF/ICSI cycle, this sample size was not high enough to detect significant differences between healthy and morbid women suffering from pathologies with low prevalence in the population. However, as the main aim of the study was to analyze the "global" effect of morbid conditions on IVF/ICSI outcomes, this is a weak limitation. Analysis of the effect of diseases with low incidence in the population on IVF/ICSI outcomes would require a multicenter or, even better, a nationwide registry study.

## Conclusion

The present study shows a significant causal association between most preexisting or concomitant diseases present at the starting time of the first intended oocyte retrieval cycle and lower odds of cumulative live birth, i.e., decreased fecundity, in the first IVF/ICSI cycle. These results complement a previous study [1] showing that different infertility etiologies are genetically and clinically linked with other diseases appearing after infertility is manifested. Data from both studies suggest the existence of a reciprocal correspondence between women's fecundity potential and morbid conditions. Note that the concept of linking particular morbid conditions with fecundity potential may also include non-morbid phenotypic traits such as facial attractiveness, general intelligence, BMI, pigmentary traits of hair, eyes and skin, voice pitch, handgrip strength, etc. [1]. Non-morbid phenotypic traits may be a third player in the approach of searching common pathogenic mechanisms that link diseases together in single meta-diseases [17]. Further work is needed to uncover this three-way relationship in both women and men.

## Compliance with ethical standards

This study was approved by the Ethical Committee of Clinical Investigation, Valencia University Clinical Hospital on November 30th 2017 (2017/316).



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